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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/021,410	02/10/98	RIGLER R	P58841US1

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EXAMINER	
PHAM, M	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95) **1- File Copy**

Office Action Summary	Application No. 09/021,410	Applicant(s) Rigler et al.
	Examiner First Last	Group Art Unit 1234

☒ Responsive to communication(s) filed on *Feb 10, 1998*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *85-118* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *85-118* is/are rejected.

☒ Claim(s) *90 and 95* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☒ The drawing(s) filed on *Feb 10, 1998* is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Specification

1. If applicant continues to prosecute the application, revision of the specification and claims to present the application in proper form is required. While an application can be amended to make it clearly understandable, no subject matter can be added that was not disclosed in the application as originally filed. The specification should be divided into sections as described below. Further, the specification lacks a Brief Description of the Drawings section.

2. Applicant is advised on how to arrange the content of the specification.

Content of Specification

(a) Title of the Invention: See 37 CFR 1.72(a). The title of the invention should be placed at the top of the first page of the specification. It should be brief but technically accurate and descriptive, preferably from two to seven words.

(b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See MPEP § 310.

(d) Reference to a "Microfiche Appendix": See 37CFR 1.96© and MPEP § 608.05. The total number of microfiche and the total number frames should be specified.

(e) Background of the Invention: The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: A brief summary or general statement of the invention as set forth in 37 CFR 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(g) Brief Description of the Several Views of the Drawing(s): A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

(h) Detailed Description of the Invention: A description of the preferred embodiment(s) of the invention as required in 37 CFR 1.71. The description should be as short and specific as is necessary to describe the invention adequately and accurately. This item may also be titled "Best Mode for Carrying Out the Invention." Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(I) Claim or Claims: See 37 CFR 1.75 and MPEP § 608.01(m). The claim or claims must commence on separate sheet. (37 CFR 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps.

(j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 250 words or less on a separate sheet following the claims.

(k) Drawings: See 37 CFR 1.81, 1.83-1.85, and MPEP § 608.02.

(l) Sequence Listing: See 37 CFR 1.821-1.825.

3. The abstract of the disclosure is objected to because the invention as claimed pertains only to a device for performing fluorescence correlation spectroscopy, while the abstract describes the device and a method for identifying one or a small number of molecules. Correction is required. See MPEP § 608.01(b).

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

6. The following title is suggested: A device for the evaluation of biopolymer fitness.

7. Claim 95 is objected to because of the following informalities: the phrase "...generated due excitation..." should be "...generated due to excitation..." . Appropriate correction is required.

8. Claim 90 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 90 does not differ substantially from claim 88; therefore, claim 90 fails to further limit the claim on which it depends.

Drawings

9. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

10. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: 54 referred to on page 72, line 20. Correction is required.

11. The drawings are objected to because the y-axis label is not present in Figure 17a and b. Correction is required.

12. Applicant is required to submit a proposed drawing correction in reply to this Office action. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 85-118 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitations of "preferably", "in particular", "optionally", and "especially" throughout the claims render the claims vague and indefinite. These terms do not limit the claims because they convey optional limitations; therefore, their use is confusing.

b. The recitation of "and/or" throughout the claims render the claims vague and indefinite because it is not clear what the applicant intends to be encompassed by the claims.

c. The terms "small" in claim 85 and "high" in claim 99 is a relative term which render the claim indefinite. The term is not defined in the claims or the specification. Further, one of ordinary skill in the art would not be able to determine the scope of the invention.

d. The unit "μm" in claim 85 is not defined in the claims or in the specification; therefore, it renders the claim indefinite. It is not clear whether the unit in micrometer (micron) or micromolal. If the unit is micromolar, then the abbreviation should be "μM", not "μm'.

e. The volume unit "1" in claim 85 is not defined in the claims or the specification; therefore, it renders the claim indefinite. This unit is not a commonly known or acceptable unit of volume.

f. The phrase "such as" in the claims renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

g. Claim 85 recites the limitation "the focusation", " the laser light excitation", "the object plane", "the beam path", and "the fluorescent radiation" in lines 7, 12, 14, and 15, respectively. There is insufficient antecedent basis for this limitation in the claim.

h. Claim 86 recites the limitation "the object plane" in line 2. There is insufficient antecedent basis for this limitation in the claim.

i. Claim 87 recites the limitation "the optics" in line 1. There is insufficient antecedent basis for this limitation in the claim.

j. Claim 105 recites the limitation "the detectors" in line 1. There is insufficient antecedent basis for this limitation in the claim.

k. Claims 96, 97, 100-105, and 107 recites numbers from the figures. It is not clear what these numbers are referring to. These numbers should be remove from the claim to obviate the rejection.

l. Claim 99 recites the phrase "per se" in line 1. The phrase is redundant in the context that it is being used and should be removed to obviate the rejection.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

16. Claims 85, 90- 94, are rejected under 35 U.S.C. 102(b) as being anticipated by Rigler et al., Kask et al., Sorscher et al., Thompson et al., or Myer et al.

17. Rigler et al., Kask et al., Sorscher et al., Thompson et al., or Myer et al. disclose a FCS apparatus wherein the apparatus comprises a laser beam generator, a focusing lens, a dichroic (semitransparent) mirror, a fluorescence detector, and a pinhole aperture. Therefore, Rigler et al., Kask et al., Sorscher et al., Thompson et al., Myer et al., anticipate the instant invention as claimed.

18. Claims 85, 87, 92-94 are rejected under 35 U.S.C. 102(b) as being anticipated by Rigler et al.

Rigler et al. disclose a FCS apparatus wherein the apparatus comprises a laser beam generator, a focusing lens, a dichroic (semitransparent) mirror, a fluorescence detector, and a pinhole aperture. Furthermore, Rigler et al. use a numerical aperture of 1.2. Therefore Rigler et al. anticipate the instant invention as claimed.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 89, 90, 99-100, 107, 109, 101-102 and 110 rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al. in view of Sorscher et al.

See above for the disclosure of Rigler et al.

Rigler et al., however, differs from the claimed invention because they do not show a prefocusing device to prefocus the laser beam.

Sorscher et al. disclose a FCS device comprising a prefocus lens (see Figure 1), and microscope optics wherein the laser emits wavelengths >200 nm (see page 29, Description of the Apparatus).

Therefore, it would have been obvious to one of ordinary skill the art at the time the invention was made to incorporate a prefocus lens in the apparatus of Rigler et al. to prefocus the laser beam before the focus lens, and to incorporate microscope optics to focus the emitted light to the detector, as per the teaching of Sorscher. One of ordinary skill in the art would be motivated to incorporate a prefocus lens and microscope optics in the device of Rigler et al. because it would have been easier to use available microscope optics than to fabricate the devices.

21. Claims 103-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al. in view of Sorscher et at. as applied to claims 89, 90, 99-100, 107, 109, and 110 above, and further in view of Hirshfeld (U.S. Pat. 3,872,312).

See above for the disclosure of Rigler et al. in view of Sorscher et at.

Rigler et al. and of Sorscher et at., however, differs from the claimed invention in that the do not disclose the apparatus wherein the emitted light beam passes the imaging lenses, beam splitter, and filter element prior to the detection unit which comprises two detectors.

Hirshfeld disclose an optical apparatus wherein the emitted light beam passes the imaging lenses, beam splitter, and filter element prior to the detection unit which comprises at least two detectors (see Figure 1). By splitting the emitted light and sending it to two different detectors, Hirshfeld is able to detect two different emitted wavelengths of light.

Therefore, it would have been obvious to one of ordinary skill the art, motivated by the desire to detect two different emitted wavelengths of light, at the time the invention was made to incorporate an imaging lens, a beam splitter, a filter element, and two detectors in the apparatus of

Rigler et al. to detect two different emitted wavelengths of light, as per the teaching of Hirshfeld. The advantage of being able to detect two different emitted wavelengths is that it is posible to obtain more than one information from the sample.

22. Claim 86, and 95-98 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al. in view of Eigen et al.

See above for the disclosure of Rigler et al.

Rigler et al., however, differs from the claimed invention because they do not disclose the use of two laser beams, two focusing devices, two detector devices, and a correlator.

Eigen et al. disclose an FCS apparatus for cross correlation analysis comprising two lasers at different wave lengths and two detectors (see Figure 6). Eigen et al. also disclose the importance of a small measuring volume in detecting a single molecule (see page 5742, Small Volume Elements with High Quantum Flux). According to Eigen et al., the volume must be small enough so that (I) the signal to noise ratio allows the detection of single quantum bursts of fluorescent light, (II) the diffusion times of the target molecules within the measuring volume is kept short enough to prevent bleaching of the dye, and (III) the target molecules are minimized in the measuring volume at any time to make it possible to associate quantum bursts with single molecule.

Therefore, it would have been obvious to one of ordinary skill the art at the time the invention was made to incorporate the double beam apparatus of Eigen et al. into the apparatus of

Rigler et al. to excite a sample with two different wavelengths so that two analytes can be measured using two different dyes.

Further, although Eigen et al. do not teach the specific image scale, sample volume, and aperture diameter, the optimum image scale, sample volume, and aperture can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art.

From the layout of the device in Figure 6 of Eigen et al., the construction and arrangement of the device in claim 96-97 would be obvious to to one of ordinary skill in the art.

23. Claim 98 rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al. in view of Eigen et al. as applied to claim 95 above, and further in view of Meyer et al.

See above for the disclosure of Rigler et al. and Eigen et al.

Rigler et al. and Eigen et al., however, differ from the claimed invention because they do not disclose that the objective lens can be positioned by an adjusting element.

Meyer et al. disclose an FCS apparatus wherein the focusing lenses are adjustable using an adjusting element (see Figure 2).

Therefore, it would have been obvious to one of ordinary skill the art at the time the invention was made to incorporate the focusing lens of Meyer et al. into the FCS apparatus of Rigler et al., as modified by Eigen et al., because the focusing lens of Meyer et al. provides the advantage of being adjustable so that adjustments can be made to better focus the lens unlike the fixed objective lens in the apparatus of Rigler et al.

24. Claims 111-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al. in view of Sorscher et al. as applied to claims 89, 90, 99-100, 107, 109, and 110 above, and further in view of Eigen et al.

See above for the disclosures of Rigler et al. and Sorscher et al.

Rigler et al. and Sorscher et al., however, differs from the claimed invention because they do not disclose the use of capillary electrophoresis, electric trap, and two microscope optics facing each other to enclose the measuring compartment.

Besides the disclosure described above, Eigen et al., also disclose an FCS apparatus comprising two microscope optics facing each other (see Figure 6). Further, Eigen et al. teach the importance of capillary electrophoresis and electrical trapping to separate unbound fluorescent label from its target molecule, wherein the fluorescent label and its target molecule have the same electrical charge (see page 5745, Electrical Trapping).

Therefore, it would have been obvious to one of ordinary skill the art at the time the invention was made to incorporate, in an FCS apparatus, two microscope optics facing each other to focus two different emitted wavelengths of light to different detectors, and capillary electrophoresis and electrical trapping devices to separate similarly charged fluorescent label and target molecule, as per the teaching of Eigen et al. One of ordinary skill in the art would be motivated to incorporate the teaching to Eigen et al. in the FCS apparatus Rigler et al., as modified by Sorscher et al., because, as taught by Eigen et al., using two microscope optics has the advantage of being able to detect two different wave length, and using a capillary

eletrophoresis and electrical trapping devices has the advantage of being able to separate the fluorescent molecule from the target molecule to reduce background fluorescence.

25. Claim 115-116 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al., Sorscher et al., and Eigen et al. in view of Barrett et al. (U.S. Pat. 5,252,743).

See above for the disclosures of Rigler et al., Sorscher et al., and Eigen et al.

The disclosures of Rigler et al., Sorscher et al., and Eigen et al., however, differ from the claimed invention because they do not disclose that the sample is fixed in a spatially defined position.

Barrett et al. disclose a spatially addressable method and apparatus of immobiling antibodies on a surface of solid support (or sample receiving device). By being able to form a patterned surface of preselected, spatially addressable reactive regions (or sample volumes), it is possible to screen a plurality of reactions using fluorescent labeling or other optical techniques (column 2, lines 53-68; column 3, lines 1-3).

Therefore, it would have been obvious to one of ordinary skill the art at the time the invention was made tofix a sample in a spacially defined position, as taught by Barrett et al., in the apparatus of Rigler et al., Sorscher et al., and Eigen et al. because, as taught by Barrett et al., fixing a sample in a spacially defined position provides the advantage of being able to screen a plurality of reactions.

26. Claim 116 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al., Sorscher et al., and Eigen et al. in view of Schwartz (U.S. Pat. 5,720,928).

See above for the disclosures of Rigler et al., Sorscher et al., and Eigen et al.

The disclosures of Rigler et al., Sorscher et al., and Eigen et al., however, differ from the claimed invention because they do not disclose that the sheet for receiving samples has specific binding for molecules.

Schwartz discloses the immobilization of DNA molecules on a glass chip whose surface is derivatized with 3-aminopropyltriethoxysilane (APTES), 3-methylaminosilane, or other amino-containing silane compounds to image, observe, and determine the size of individual nucleic acid molecule (see column 15, lines 44-61).

Therefore, it would have been obvious to one of ordinary skill the art at the time the invention was made to immobilize oligonucleotides or DNA molecules on a surface or sheet for receiving the samples, as per the teaching of Schwartz, to observe specific reaction or molecule using an FAS apparatus of any of the primary references. One of ordinary skill the art at the time the invention was made would be motivated to make the sheet for receiving samples has specific binding for molecules, as per the teaching of Schwartz, so that molecules can be immobilized on the sheets to simplify the detection process.

27. Claim 117 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al., Sorscher et al., and Eigen et al. in view of Dixon et al. (U.S. Pat. 5,381,224, U.S. pat. 5,760,951).

See above for the disclosure Rigler et al., Sorscher et al., and Eigen et al.

Dixon et al. disclose an optical imaging or mapping system using an appliance (two mirrors) to deflect the laser beam in defined coordinates in order to scan multiple samples (see

Abstract). In this system, the laser beam is reflected from the first mirror, which rotates on the horizontal axis, to the second mirror, which rotates on the vertical axis, before hitting the sample (see Figure 1). By using this two mirror appliance, Dixon et al. are able to focus the laser beam to a defined coordinate on the sample.

Therefore, it would have been obvious to one of ordinary skill the art at the time the invention was made to incorporate, in an FCS, the laser beam deflection appliance of Dixon et al. to focus the laser beam to a defined coordinate on the sample so that it is possible to detect a plurality of sample volumes on the same sample receiving device.

28. Claim 118 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rigler et al. in view of Gourley (U.S. Pat. 5,608,519).

See above for the disclosure of Rigler et al.

Rigler et al. differs from the claimed invention because the do not disclose a multiarray detector for detection of multiple sample volumes.

Gourley et al. disclose a laser apparatus containing an array photodetector to detect wavelengths of light from an array of samples.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made, to incorporate the detector array of Gourley et al. into the apparatus of Rigler et al. to detect several excitation volumes simultaneously. One of ordinary skill in the art at the time the invention was made would be motivated to use a detector array in the FCS device of

Rigler et al., because the detector array, as taught by Gourley et al., has the advantage of being able to simultaneously detect several excitation volumes.

Conclusion

29. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Iketaki et al. (U.S. Pat. 5,835,262) is cited to show a multi-wavelength optical microscope. Although Iketaki et al. specifically describe a two-wavelength optical microscope, they also disclose that three or more wavelengths may be used to illuminate a sample.

Elofsson et al. (1991), *Biochemistry*, 30:9648-9656 is cited to show the use of fluorescence spectroscopy to study picosecond fluorescence of *E. coli* thioredoxin.

Hirschfeld (U.S. Pat. 3,872,312) is cited to show an optical apparatus for detecting and classifying virus particle using fluorescence spectroscopy.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Minh-Quan Pham whose telephone number is (703) 305-1444. The examiner can normally be reached Monday through Friday from 8:00 AM to 4:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reach at (703) 308-4027. The fax number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Minh-Quan Pham, Ph.D.

September 30, 1999

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641